Notice of Allowability	Application No.	Applicant(s)	
	09/582,863	GUSTAFSSON, DAVID	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/10/05*.

2. ☒ The allowed claim(s) is/are *20,22-43,46-49 and 51-57*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☒ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)). Sweden 9901442-5

   * Certified copies not received: *Sweden 9904419-0*.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 6/5/03
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20050505* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Leonard Mitchard on May 13, 2005.

Examiner's Amendments to the Specification:

Please insert the following paragraph after the title at page 1:

This application is a 371 of PCT/SE00/00756, filed April 19, 2000, which claims priority of Sweden Application No. 9901442-5, filed April 21, 1999, and Sweden Application No. 9904419-0, filed December 3, 1999.

Examiner's Amendments to the Claims:

Claim 20, 28, 31, 32 and 41 have been amended as follows:

20 (Currently amended). A kit of parts comprising:

(a) a pharmaceutical formulation ~~including~~ comprising a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable salt~~,~~ or solvate thereof ~~or a pharmaceutically acceptable derivative, said derivative having the inhibitory activity against thrombin~~, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation ~~including~~ comprising a prodrug of the low molecular weight thrombin inhibitor of formulation (a), or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

which formulations (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

28 (Currently amended). The kit of parts as claimed in Claim 20, 24 or 27, wherein the formulation comprising thrombin inhibitor, or salt~~,~~ or solvate thereof ~~or a pharmaceutically acceptable derivative, said derivative having the inhibitory activity against thrombin,~~ is a parenteral formulation and that comprising the prodrug, or salt or solvate of said prodrug, is an oral formulation.

31 (Currently amended). A pharmaceutical formulation ~~including~~ comprising:

(i) a low molecular weight thrombin inhibitor or a pharmaceutically acceptable salt~~,~~ or solvate thereof ~~or a pharmaceutically acceptable derivative, said derivative having the inhibitory activity against thrombin~~; and

(ii) a prodrug of the low molecular weight thrombin inhibitor of component (i) or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with

(iii) a pharmaceutically acceptable adjuvant, diluent or carrier.

32 (Currently amended). A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

(a) a pharmaceutical formulation ~~including~~ comprising a low molecular weight thrombin inhibitor, or a pharmaceutically acceptable salt~~,~~ or solvate thereof ~~or a pharmaceutically acceptable derivative, said derivative having the inhibitory activity against thrombin~~, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, in conjunction with

(b) a pharmaceutical formulation ~~including~~ comprising a prodrug of the low molecular

weight thrombin inhibitor of formulation (a), or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

to a patient suffering from, or susceptible to, such a condition in an effective amount and for a time and under conditions suitable for reducing the incidence of said condition.

41 (Currently amended). A method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

(a) a pharmaceutical formulation ~~including~~ comprising melagatran, or a pharmaceutically acceptable salt~~,~~ or solvate thereof ~~or a pharmaceutically acceptable derivative, said derivative having the inhibitory activity against thrombin~~, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, in conjunction with

(b) a pharmaceutical formulation ~~including~~ comprising a prodrug of formula

R^1O_2C-CH_2-(*R*)Cgl-Aze-Pab-OH,

wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab, or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

to a patient suffering from, or susceptible to, such a condition in an effective amount and for a time and under conditions suitable for reducing the incidence of said condition.

The following is an **Examiner's Statement of Reasons for Allowance**: The following reference appears to be the closest art to the claimed invention: Lam *et al.* (U.S. Patent 6,602,871 B2, priority date December 23, 1998) teach a nitrogen-containing aromatic heterocycle with ortho-substituted groups such as compound of formula (I) or its prodrug thereof as a factor Xa or thrombin inhibitor, and the compound can be administered alone or in combination with one or more additional therapeutic agents such as a thrombin inhibitor or its prodrug in a pharmaceutical composition for treating thromboembolic disorders such as deep vein thrombosis. However, the reference does not teach the use of a combination of a low molecular weight thrombin inhibitor with the prodrug of the same thrombin inhibitor in treating thromboembolic disorders. Antonsson et al. (WO 97/23499) teach oral or parenteral administration of active thrombin inhibitors may lead to undesirable local bleeding as a result of a high local concentration (page 3, lines 22-24), thus the use of the prodrug may avoid the potential complications caused by an active thrombin inhibitor (page 22, lines 11-19); and the specification teaches the prodrug of a low molecular weight thrombin inhibitor is metabolized in vivo to form a low molecular weight thrombin inhibitor within a predetermined time (page 10, line 14-27), thus the combination of a low molecular weight thrombin inhibitor and its prodrug in the treatment would maintain the drug efficiency and avoid the complication of using only active thrombin inhibitor in the treatment. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
May 12, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER